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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,040	11/15/2000	Paul J. Carter	11669.185USD3	5212

7590 07/31/2007

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
07/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/714,040	CARTER, PAUL J.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,39-44,49-51 and 54-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40-42* is/are allowed.

6)☒ Claim(s) *25,39, 43-44,49-51 and 54-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 April 2007 has been entered.

2. Claims 1-24, 26-38, 45-48 and 52-53 are cancelled.
Claims 25, 44, 49, 54, 58, 60 and 64 have been amended.
Claims 66-67 have been added.

3. Claims 25, 39-44, 49-51 and 54-67 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections

Rejections Withdrawn

6. The rejection of claims 52-57, 59-63 and 65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing mew matter is withdrawn in view of the cancellation of the claims 52-53 and the amendments to claims 54-57, 59-63 and 65.

Rejections Maintained/New Grounds of Rejections

7. The rejection of claims 25, 39, 43-44, 49-51, 58, 64 and now applied to newly added claims 66-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing mew matter is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As presently amended, the claims are drawn to a composition comprising a monospecific F(ab')2 that comprises a first and second Fab' each comprising a single hinge region cysteine residue and comprising a C-terminal amino acid sequence of Cys-Ala-Ala. The claims also recite Fab' and F(ab)2 fragments wherein the CH1 domain is fused to one or more cysteines or a cysteine-containing polypeptide of about 1-10 amino acid residues in place of an immunoglobulin hinge and wherein the cysteine containing polypeptide has a single cysteine residue, or wherein the Fab' comprises a C terminal amino acid sequence Cys-Ala-Ala. Again, there is insufficient written support for the limitation of a CH1 fused to one or more cysteines or a cysteine- containing polypeptide of about 1-10 amino acids that comprise a C-terminal sequence of Cys-Ala-Ala. Further, there is insufficient written support for the limitation wherein each Fab' has a single hinge region cysteine residue and comprises a C terminal amino acid sequence of Cys-Ala-Ala. It is reiterated that the as filed specification discloses at pg. 11 that the Cys-X-X sequence where X is preferably Ala is fused to the C-terminus of the CH1 of Fab'. Further, at pg. 20, lines 4-7, the specification discloses that the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala. The only disclosure of 10 amino acid residues is found at pg. 11, lines 25-27, where it is disclosed that the hinge may be entirely omitted in favor of one or more cysteine residues or, preferably short (about 1-10 residues) cysteine-containing polypeptide. Thus, the specification as filed as it pertains to the CysAlaAla sequence only provides adequate written support for a F(ab')2 comprising a first and second Fab' each comprising a CH1 domain fused to the amino acid sequence Cys-Ala-Ala (i.e., claims 40-41). Additionally, the as filed specification discloses at pp. 29-30 that in order to express the Fab' fragment of huMab4D5-8 the CH1 gene segment was extended to encode part of the cysteine-containing antibody hinge region where cysteine followed by two prolines and another cysteine was chosen (CPPC). To prevent the formation of an intramolecular disulfide bond between the two cysteine residues of the CPPC sequence construction of a Fab' variant with a single hinge cysteine residue having the C-terminal sequence Cys-Ala-Ala was produced (see pg. 30, lines 23-27). Thus, there is insufficient written support for the limitation that each

Fab' has a single hinge cysteine residue and comprises a C terminal amino acid sequence of Cys-Ala-Ala. Further, while the Fab' variant comprising the CH1-Cys-Ala-Ala sequence, which is three amino acids in length and is a single species within the subgenus of a CH1 domain fused to up to 10 amino acids comprising the C-terminal sequence Cys-Ala-Ala, this does not provide adequate written support for the broader subgenera of monospecific F(ab)2 wherein each Fab' has a single hinge cysteine residue and comprises a C terminal amino acid sequence of Cys-Ala-Ala, or Fab' and F(ab)2 fragments wherein the CH1 domain is fused to one or more cysteines and comprises a C terminal amino acid sequence Cys-Ala-Ala, or a cysteine-containing polypeptide of about 1-10 amino acid residues in place of an immunoglobulin hinge and wherein the cysteine containing polypeptide has a single cysteine residue and wherein the Fab' comprises a C terminal amino acid sequence Cys-Ala-Ala as presently claimed (i.e., claims 66-67) because there is insufficient guidance and direction to these limitations as currently claimed. A subgenus is not necessarily described by a genus encompassing it and a species upon which it reads. *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Further, it is noted that a hinge region or polypeptide comprising a single cysteine residue and the C terminal sequence Cys-Ala-Ala would comprise two cysteines. The Instant claims recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112. Applicant is required to provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

Response to Arguments

The response filed 4/23/2007 reviews what each of the claims as presently amended are drawn to. At pg. 10 of the response applicant states that the language in claims 25, 44 and 49 is language which appears in the specification at least on pg. 30,

lines 26-27. This is not found persuasive because the disclosure of a Fab' variant with a single hinge cysteine residue having the C-terminal sequence, CysAlaAla is consistent with examiners position of a Fab' variant wherein the sequence Cys-Ala-Ala is the hinge region sequence linked to the CH1 domain. This does not provide adequate written support for the subgenus of hinge region sequences that have a single hinge region cysteine AND comprises a C terminal amino acid sequence of CysAlaAla, meaning that the hinge region contains two cysteine residues. Applicant again argues that the specification at pg. 11 provides adequate written support for the currently claimed limitations. This has been fully considered but is not found persuasive. Again, the as filed specification discloses at pg. 11 that the Cys-X-X sequence where X is preferably Ala is fused to the C-terminus of the CH1 of Fab'. Further, at pg. 20, lines 4-7, the specification discloses that the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala. Thus, the disclosure of the C-terminus of the CH1 of Fab' as being fused to the sequence Cys-Ala-Ala, or a single species falling within the presently claimed subgenus, does not provide sufficient guidance and direction to the broader scope of the claims encompassing the CH1 domain of Fab' fused to a sequence that has a single hinge region cysteine residue AND comprises a C terminal sequence of CysAlaAla. Thus, while applicant has disclosed at pg. 11 that the Fab' having at least one hinge cysteine present at the C terminus of the heavy chain as part of a variant hinge or part of a short (i.e., about 1 to 10 residues) cysteine containing polypeptide in place of the hinge region, this does not provide adequate written support for said variant hinges or said cysteine containing polypeptides that comprise the C terminal sequence of CysAlaAla because as noted by applicant "the C terminus of the CH1 of Fab' is fused to the sequence Cys-X-X, wherein X is Ala or may be any other residue such as Arg, Asp,, or Pro and one or both X amino acids may be deleted" (e.g., pg. 11 of the response). Applicants' reliance on a generic disclosure and possible a single or limited species has not provided sufficient direction and guidance to the "features" currently claimed. It is noted that a generic or sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily

described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Again, the as filed specification discloses at pg. 11 that the Cys-X-X sequence where X is preferably Ala is fused to the C-terminus of the CH1 of Fab'. Further, at pg. 20, lines 4-7, the specification discloses that the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala. Thus, the disclosure of the C-terminus of the CH1 of Fab' as being fused to the sequence Cys-Ala-Ala, or a single species falling within the presently claimed subgenera, does not provide sufficient guidance and direction to the broader scope of the claims encompassing the CH1 domain of Fab' fused to one or more cysteines and comprising a C terminal amino acid sequence Cys-Ala-Ala, or fused to a single cysteine-containing polypeptide of about 1-10 amino acid residues in place of an immunoglobulin hinge wherein the Fab' comprises a C terminal amino acid sequence Cys-Ala-Ala. Obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter, which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Applicant points to original claim 11 which discloses a Fab' comprising a C-terminal amino acid sequence Cys-Ala-Ala and at pg. 30, lines 26-27 of the specification as filed discloses making a Fab' variant with a single hinge cysteine residue having a C-terminal amino acid sequence Cys-Ala-Ala. This has been fully considered but is not found persuasive. Again, the as filed disclosure of a Fab' comprising a C-terminal amino acid sequence Cys-Ala-Ala does not provide adequate written support for the broader limitations of each Fab' having a single hinge cysteine residue and comprising a C terminal amino acid sequence of CysAlaAla, or comprising one or more cysteines and comprising a C terminal amino acid sequence Cys-Ala-Ala, or comprising a single cysteine-containing polypeptide of about 1-10 amino acid residues in place of an immunoglobulin hinge wherein the Fab' comprises a C terminal amino acid sequence Cys-Ala-Ala. Further, applicants' working example in the specification where the sequence cysteine followed by two prolines and another cysteine (CPPC sequence;

found in the naturally occurring human IgG1 hinge region) was selected and used to extend the CH1 domain of huMab4D5-8 and the subsequent replacement of this sequence with Cys-Ala-Ala to preclude intrachain disulfide bond formation (i.e., see example at pg. 29, lines 30-35 and pg. 30, lines 17-29), does not provide adequate written support for the broader limitation of a Fab' having a single hinge cysteine residue and comprising a C terminal amino acid sequence of CysAlaAla because there is no description of what additional sequence in addition to the Cys-Ala-Ala is contained therein. Adequate written description does not extend to that which could have been disclosed but was not. Further, the disclosure that the human IgG1 sequence CPPC was selected and used to extend the CH1 domain of Fab' and the subsequent replacement of this sequence with Cys-Ala-Ala to preclude intrachain disulfide bond formation does not convey any other sequence or structure other than Cys-Ala-Ala as being fused to the CH1 domain of Fab'. The as filed disclosure does not clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed.

With respect to claims 58, 64 and newly added claims 66-67, the claims recite the limitation wherein the antibody fragment is a Fab' in which a heavy chain CH1 domain is fused to one or more cysteines, or a cysteine-containing polypeptide of about 1-10 residues, and wherein the Fab' comprises a C-terminal amino acid sequence of Cys-Ala-Ala or wherein the short cysteine containing polypeptide comprises a part of a hinge region and has all of the hinge region cysteines C-terminal to the first cysteine deleted. At pg. 13 of the response, applicant points to pg. 6, lines 30-31 and pg. 11, lines 24-27 as disclosing a species of Fab' having the claimed characteristics. This has been fully considered but is not found persuasive. For reasons set forth above, the as filed disclosure does not provide adequate written support for the present claim limitations, which encompass compositions comprising a Fab' in which the CH1 domain is fused to one or more cysteines, or a cysteine-containing polypeptide of about 1-10 residues and a C-terminal sequence of Cys-Ala-Ala, or wherein the short cysteine containing polypeptide comprises a part of a hinge region and has all of the hinge region cysteines C-terminal to the first cysteine deleted. Again, the disclosure of the

sequence Cys-Ala-Ala fused to the C-terminus of the CH1 of Fab' (e.g., specification at pg. 11, lines 32-35), the disclosure where the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala (specification at pg. 20, lines 4-7) and the disclosure of a Fab' comprising the C-terminal sequence Cys-Ala-Ala (e.g., original claim 11) does not provide adequate written support for (i) the fusion of the CH1 domain of Fab' to one or more cysteines and comprising a C-terminal sequence of Cys-Ala-Ala, (ii) the fusion of the CH1 domain of Fab' to a single cysteine-containing polypeptide of about 1-10 residues and comprising a C-terminal sequence of Cys-Ala-Ala, or (iii) the fusion of the CH1 domain of Fab' to part of a hinge region that has all of the hinge region cysteines C-terminal to the first cysteine deleted. Further, as noted in Fig. 1 of Bodmer et al (WO 89/01974, 3//1989, cited on PTO-892 mailed 4/20/2005), the first hinge region cysteine of human IgG1 forms a disulfide bond with the light chain. Thus, deletion of all cysteines C terminal to this first cysteine in human IgG1 would not yield F(ab')2. Again, a generic or sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter, which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

For these reasons and those already of record, the rejection of claims 25, 39, 43-44, 49-51, 58, 64 and 66-67under 35 U.S.C. 112, first paragraph, as introducing mew matter is maintained.

New Grounds of Objections/Rejections

8. Claims 43 and 59 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper

dependent form, or rewrite the claim in independent form. Base claim 25 from which claim 43 depends recites "wherein the monospecific F(ab)2 lacks glycosylation". Thus, the recitation of "wherein the F(ab)2 lacks glycosylation in dependent claim 43 does not add a limitation to the base claim from which it depends and as such does not further limit base claim 25. Similarly, base claim 54 from which claim 59 depends recites "wherein the Fab' lacks glycosylation", and hence the limitation "wherein the Fab' lacks glycosylation" in dependent claim 59 does not further limit base claim 54. The fourth paragraph of 35 U.S.C. states that a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

9. Claims 25, 39, 43-44, 49-51 and 54-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 25, 39, 43-44 and 49-51 are indefinite in the recitation "has a single hinge region cysteine residue and comprises a C terminal amino acid sequence of Cys-Ala-Ala " in claims 25, 44 and 49. Is the Cys-Ala-Ala sequence in addition to the single hinge region cysteine residue as presently claimed, or is the cysteine of the sequence Cys-Ala-Ala the single hinge region cysteine residue, or is some other meaning contemplated by the phrase. As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

b. Claim 25 recites the limitation "the cysteine of the first Fab'" and "the cysteine of the second Fab'". There is insufficient antecedent basis for this limitation in the claim. Claim 25 recites that each Fab' has a singe hinge cysteine AND comprises a C terminal amino acid sequence of Cys-Ala-Ala, making it unclear which cysteine is being referenced, the cysteine of the hinge region or the cysteine in the Cys-Ala-Ala sequence. See MPEP 2173.05(e).

c. Claims 54-59 are indefinite in the recitation "Fab' fragment...wherein the nucleic acid encodes a light chain variable domain, a heavy chain variable domain and a CH1 domain fused to one or more cysteines...in a microbial host under conditions suitable for secretion of the antibody fragment into the periplasmic space" in claim 54. The specification at pg. 2 and as known by those skilled in the art, a Fab fragment also contains the constant domain of the light chain. Does the nucleic acid encode a light chain variable domain and the light chain constant domain or is the claimed antibody not a Fab' fragment? Further, are the light and heavy chain regions encoded on a single nucleic acid or are each of the light and heavy chains separately fused to a bacterial signal sequence? The specification also discloses that the light and heavy chains of the Fab' fragment are synthesized in reduced form and preceded by bacterial signal sequences to direct secretion into the periplasmic space of *E. coli* where the redox environment favors disulfide bond formation and the light and heavy chains may assemble, i.e., Fab' fragment formation (see pg. 3, lines 27-33 and pg. 29, lines 23-25). Is the antibody fragment, i.e., Fab' fragment assembled prior to secretion, or are the heavy and light chains preceded by bacterial signal sequences, secreted and assembled by disulfide bond formation?

d. Claims 60-67 are indefinite in the recitation "monospecific F(ab')2 produced by the process of expressing a nucleic acid...wherein the nucleic acid encodes a Fab' in a microbial host cell under conditions suitable for secretion of the Fab' into the periplasmic space" in claim 60. The specification discloses that the light and heavy chains of the Fab' fragment are synthesized in reduced form and preceded by bacterial signal sequences to direct secretion into the periplasmic space of *E. coli* where the redox environment favors disulfide bond formation and the light and heavy chains may assemble, i.e., Fab' fragment formation (see pg. 3, lines 27-33 and pg. 29, lines 23-25). Thus, given that a Fab' fragment is formed via disulfide bond formation and is not a polypeptide fusion of the heavy and light chains, it is unclear what is contemplated by a nucleic acid that encodes a Fab'. Further, is the Fab' fragment assembled prior to secretion to the periplasmic space, or are the heavy and light chains preceded by bacterial signal sequences, secreted and assembled by disulfide bond formation?

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 54-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodmer et al (WO 89/01974, 3//1989, cited on PTO-892 mailed 4/20/2005) in view of Better et al (Science, 240:1041-1043, May 20, 1988, IDS reference 24 filed 11/15/2000) as evidenced by Pluckthun et al (Immunotechnology, 3,:83-105, 1997).

Bodmer et al teach Fab' and F(ab')2 fragments comprising a hinge region in which the number of cysteines is reduced to one, which has the advantage that it will facilitate assembly of the Fab' and F(ab')2 fragments and Bodmer teaches the natural human IgG hinge sequences and states that from the known amino acid sequence it will be readily possible for the skilled person to design variants with cysteine mutations or deletions (see entire document, particularly pp. 7, 10 and Figure). Bodmer et al also teaches the attachment of reported molecules including a radionuclide to the Fab' and F(ab')2 fragments for therapy or diagnosis (see pp. 4-5 and 7). Bodmer et al do not specifically teach the expression of the Fab' and F(ab')2 fragments in *E. coli.* This deficiency is made up for in the teachings of Better et al.

Better et al teach the expression of Fab' fragments in bacteria, and bacterial produced Fab' provides a consistent, homogeneous preparation which avoids protein heterogeneity that results from nonspecific cleavages and differences in susceptibility of antibodies to protease cleavage are obviated and functional Fab' fragments provide a useful diagnostic reagent (see entire document). As evidence by Pluckthun, glycosylation does not take place in prokaryotic host cells such as *E. coli* (e.g., see pg. 88, 1st col.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced Fab' and F(ab')2 fragments comprising a hinge region having a single cysteine residue in *E. coli* wherein the Fab' and F(ab')2 fragments are linked to a reporter molecule for therapeutic benefit.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced Fab' and F(ab')2 fragments comprising a hinge region having a single cysteine residue in *E. coli* wherein the Fab' and F(ab')2 fragments are linked to a reporter molecule for therapeutic benefit in view of Bodmer et al and Better et al because Bodmer et al teach Fab' and F(ab')2 fragments comprising a hinge region in which the number of cysteines is reduced to one, which is advantageous in that a single hinge cysteine facilitates assembly of the Fab' and F(ab')2 fragments and Bodmer teaches the natural human IgG hinge sequences and states that from the known amino acid sequence it will be readily possible for the skilled person to design variants with cysteine mutations or deletions and Better et al teach the expression of Fab' fragments in bacteria, and bacterial produced Fab' provides a consistent, homogeneous preparation which avoids protein heterogeneity that results from nonspecific cleavages and differences in susceptibility of antibodies to protease cleavage are obviated and functional Fab' fragments provide a useful diagnostic reagent and Bodmer et al teaches linking the Fab' and F(ab')2 fragments to a reporter molecule, including a radionuclide for diagnosis. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to reduce the number of hinge cysteines of Fab' and

F(ab')2 fragments to one in order to facilitate assembly and produce the single hinge cysteine Fab' and F(ab')2 fragments in *E. coli* because bacterial produced Fab' provides a consistent, homogeneous preparation which avoids protein heterogeneity that results from nonspecific cleavages and obviates differences in susceptibility of antibodies to protease cleavage and as evidenced by Pluckthun et al, the *E. coli* produced Fab' and F(ab')2 fragments would necessarily lack glycosylation, since glycosylation does not take place in prokaryotic host cells. Further, one of ordinary skill in the art at the time the invention as made would have been motivated to link a reporter molecule, including a radionuclide to the single hinge cysteine Fab' and F(ab')2 fragments for use as a diagnostic reagent. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker,* 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced Fab' and F(ab')2 fragments comprising a hinge region having a single cysteine residue in *E. coli* wherein the Fab' and F(ab')2 fragments are linked to a reporter molecule for therapeutic benefit in view of Bodmer et al and Better et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claims 40-42 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643